IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application of:	Rittershaus and Thomas	
Serial No.:	09/943,334	**ON APPEAL**
Filed:	August 30, 2001	Group Art Unit: 1644
Entitled:	MODULATION OF CHOLESTERYL ESTER TRANSFER PROTEIN (CETP) ACTIVITY	Examiner: M. Belyavskyi

Atty. Docket No.: TCS-411.1P US-1

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF

Sir:

Pursuant to 37 C.F.R. §1.193(b), Appellants submit this Reply Brief in triplicate, responding to issues raised in the Examiner's Answer mailed April 23, 2004 in the above-identified patent appeal.

This Reply Brief is filed simultaneously with Appellants' Request for an Oral Hearing and the filing fee specified under 37 C.F.R. §1.17(d). The Commissioner is authorized to charge any additional fees required in connection with the filing of this Reply Brief or the accompanying Request to PTO Deposit Account No. 50-0268.

STATUS OF CLAIMS

The Examiner states that the Appellants' statement of the status of the claims contained in the Brief is "substantially correct". Inasmuch as this may be interpreted by the Board as equivalent to "partially incorrect", Appellants challenge the Examiner's assertion and point out that no word of explanation or clarification is offered in support of the Examiner's characterization.

PRIOR ART OF RECORD

Appellants acknowledge the listing of references 1-6 on page 2 of the Examiner's Answer. It is noted that former reference no. 6 (U.S. 5,807,552 to Stanton et al.) has been **removed** and replaced by a **new reference** no. 6, i.e., Maillard et al., *La Presse Medicale*, 29:1731-1737 (2000) [hereinafter "Maillard"], a translation of which was supplied to Appellants.

Maillard

The Maillard document, which is not prior art to the present application, is a review of the role of Vascular Endothelial Growth Factor, or VEGF, in the process of neovascularization and angiogenesis. The article discusses administration of VEGF or gene therapy involving VEGF expression to promote collateral circulation, a speculative therapeutic approach to ischemia termed "angiogenesis therapy".

Maillard does not relate to immunology or to inhibition of CETP, therefore it is irrelevant to the present invention.

The Examiner's citation of the Maillard article appears to be for the sole purpose of incorrectly paraphrasing the third sentence of the Maillard abstract. Maillard is offered as evidence that "there is a lack in effective methods capable of preventing atherosclerosis-related conditions." (Examiner's Answer, page 5.) As discussed below, Maillard does not teach this.

Appellants' application, which was published before the Maillard article, was not cited by the authors, leading to the possibility that Maillard et al. may not have been

completely informed on the subject of effective treatments for atherosclerosis before drafting their article on the subject of artificial angiogenesis.

ISSUES ON APPEAL

(i) At page 3 of the Examiner's Answer, the Examiner refers to Appellants' persuasive argument relating to enablement with respect to how to make and use antigenic vaccine peptides according to the invention, then states that the rejection under 35 U.S.C. §112, first paragraph, stands with regard to a method of preventing atherosclerosis.

Notwithstanding the Examiner's acknowledgement of a persuasive argument, the rejection of Claims 28, 29, and 37-39 for lack of enabling disclosure was always circumscribed by the Examiner's assertion that whereas Appellants' claims for methods of treatment were enabled, Appellants' methods for prevention were not. *See*, final Office Action of April 22, 2003 at page 3. *See, also*, Appellants' statement of the issue on appeal, issue II on page 11 of the Brief.

Thus, the issue for decision on appeal with respect to enablement under 35 U.S.C. §112, first paragraph, has not changed.

(ii) At page 3 of the Examiner's Answer, the Examiner refers to Appellants' persuasive argument relating to written description of the structure of antigenic vaccine peptides according to the invention, then states that the written description rejection under 35 U.S.C. §112, first paragraph, stands only with regard to the methods of appealed Claims 28 and 29. Thus, the issue III on page 11 of Appellants' Brief may now be restated as follows:

III. Whether Appellants' specification, while being acknowledged to demonstrate that Appellants were in possession of (a) methods of treating or preventing atherosclerosis using a CETP vaccine peptide comprised of SEQ ID NO: 2, (b) methods of treating or preventing atherosclerosis using a CETP vaccine peptide comprised of a dimer of SEQ ID NO: 2, (c) methods of treating or preventing atherosclerosis using a vaccine peptide comprised of a helper T cell epitope linked to a B cell epitope comprising between 6 and 26 amino acids of the carboxy-terminal 26 amino acids of human CETP (SEQ ID NO: 1), (d) methods of treating atherosclerosis using a vaccine peptide comprising a universal helper T cell epitope linked to a B cell epitope of CETP (as defined in Claim 28), and (e) methods of treating atherosclerosis using a vaccine peptide comprising a universal helper T cell epitope linked to a B cell epitope of CETP, wherein the universal helper T cell epitope is selected from the Markush group of Claim 29, is nevertheless insufficient to demonstrate that Appellants were in possession of the methods of Claims 28 and 29 insofar as those methods recite a method for preventing atherosclerosis.

GROUPING OF THE CLAIMS

(i) With respect to the grounds of rejection under 35 U.S.C. §112, first paragraph, relating to enablement, the Examiner has asserted, at page 3 of the Examiner's Answer, that Claims 28, 29, and 37-39 must stand or fall together. This is incorrect.

Claim 28 recites a method for treating or preventing atherosclerosis comprising administering an antigenic vaccine peptide comprising a universal helper T cell epitope portion linked to a B cell epitope portion, wherein said B cell epitope portion comprises a B cell epitope of CETP.

Claim 29 recites a method according to Claim 28, wherein the universal helper T cell epitope portion is an antigenic peptide selected from a Markush group of specific helper T cell epitope peptides familiar to the art.

Claim 37 recites the method of Claim 28, wherein the B cell epitope portion of the antigenic vaccine peptide is 6 to 26 consecutive amino acids of the C-terminal 26 amino acids of human CETP.

Claim 38 recites the method of Claim 37, wherein the vaccine peptide has the amino acid sequence depicted in SEQ ID NO:2.

Claim 39 recites the method of Claim 37, wherein the vaccine peptide is a dimer of the sequence depicted in SEQ ID NO:2.

The Examiner states that these claims are of the same scope, but clearly that is incorrect. Claims that differ in scope can never stand or fall together on an issue of enablement, because the very issue raised by the rejection is whether the particular embodiment of each claim is enabled by the specification. An impermissibly overbroad claim reciting the use of any protein known to Man may not be enabled by a given specification, whereas a very narrow claim reciting the use of a single protein defined with particularity may be enabled by the same specification. On appeal, those two claims cannot stand or fall together on an issue of enablement, because the Board may find the one claim properly rejected for lack of enablement while finding the other claim adequately enabled when considered against the same disclosure. Such is the case here: Claims 28, 29, 37, 38, and 39 all differ in scope, that is, each claim contains recitations not found in any of the other claims. Since the issue of enablement must be decided by consideration of whether the method defined in each claim is described with sufficient particularity in the Appellants' specification to allow a person skilled in the art to practice that method, the issue cannot be decided by reference only to one method, e.g., the method of Claim 28.

In the present case, Claims 28, 29, 37 and 38 must be considered separately with respect to the issue of enablement. Appellants' statement in the Brief that Claims 38 and 39 would stand or fall together on the issue of enablement was a concession that if Claim 38 could possibly be found non-enabled, then the recitation of dimerization of the peptide

of SEQ ID NO:2 would not sufficiently distinguish that peptide to merit separate consideration of enablement.

(ii) With respect to the grounds of rejection under 35 U.S.C. §112, first paragraph, relating to written description, the Examiner has conceded the sufficiency of Appellants' written description for the methods recited in Claims 37, 38 and 39. With respect to the rejection of the methods for prevention of atherosclerosis defined, respectively, in Claims 28 and 29, the Examiner asserts that Claims 28 and 29 must stand or fall together. This is incorrect.

The issue for decision on appeal is whether the method defined in Claim 28 and the method defined in Claim 29 are described in the specification sufficiently to conclude that Appellants were in possession of those methods at the time their application was filed. Inasmuch as Claim 29 contains a recitation not found in Claim 28, i.e., the specific identification of a group of universal helper T cell epitope peptides for selection as a component of the vaccine peptide used according to the method, the Board must separately consider whether the additional recitation of Claim 29 demonstrates possession of the Claim 29 method by Appellants. Accordingly, Claims 28 and 29, because they define methods of differing scope, do not stand or fall together; rather, the adequacy of Appellants' written description to demonstrate possession of the method of Claim 29 must be separately considered from the adequacy of Appellants' written description to demonstrate possession of the method of Claim 28.

Nothing in Appellants' foregoing explanation of the proper grouping of the claims is to be interpreted as any sort of admission that the broader claims on appeal are inadequately enabled by the specification or insufficiently described by written description. As set forth in subsections II and III of the Argument section of Appellants' Brief, it is Appellants' position that the specification completely enables practice of each of the methods covered by the appealed claims, and that the written description demonstrates complete conception and possession of the methods of the appealed claims by Appellants at the time of filing their application. Considering the exact scope and

recitations of the claims, the enablement and written description requirements of 35 U.S.C. §112, first paragraph, have been met, and fully met, by Appellants.

(iii) With respect to the grouping of Claim 39 apart from Claims 28, 29, 37 and 38 with regard to the maintained rejections under 35 U.S.C. §103(a), the Examiner asserts that Claim 39 must stand or fall with the other claims because "[C]laim 39 is a dependent claim of the base [C]laim 28 and defines [a] similar embodiment as the base [C]laim 28." (Examiner's Answer at page 4.) This implies that if Claim 39 were amended to independent form, it would not stand or fall with the other claims. This is incorrect.

The purpose of the grouping of the claims is to clarify what will be the effect of each determination made by the Board of Appeals. If a determination of the Board with respect to one issue is dispositive of that issue for more than one claim, then those claims should be grouped together and survive together with the Board's determination of that issue. If a determination of the Board is dispositive of an issue with respect to one claim, but further aspects of that issue must be considered to dispose of that issue with respect to another claim, then those claims should not be grouped together: serial determinations of the Board are necessary to completely decide the issue with respect to all claims.

In the present case, although the grounds of rejection (35 U.S.C. §103 obviousness) are the same with respect to the rejection of Claims 28, 29, 37 and 38 on the one hand, and the rejection of Claim 39 on the other hand, Claim 39 is the subject of a separately stated rejection, relying on a different collection of citations. (*See*, final Office Action of April 22, 2003 at page 7 vs. page 11.) This being the case, Claim 39 cannot be grouped with the other claims on appeal: the Examiner himself has presented two issues for consideration on appeal, and Appellants cannot make the Board's decision on one issue apply to the separate issue raised in the final Office Action. Accordingly, Claim 39 does not stand or fall together with Claims 28, 29, 37 and 38 on the issue of obviousness.

REPY TO EXAMINER'S ARGUMENTS

I. The Substance of the Final Rejections Has Been Previously Resolved in Related Ancestor Applications, in Appellants' Favor

In addressing Appellants' point on enablement that the present claim language conforms to the language found in patents issued on Appellants' ancestor applications (Tabs B and C of the Brief), the Examiner has pointed out (page 15 of the Answer) that U.S. 6,410,022 (Tab B of the Brief) has claims directed only to treatment of atherosclerosis (not prevention) and that the defined antigenic vaccine peptides recite a B cell epitope portion comprised of 6 to 26 consecutive amino acids of the C-terminal 26 amino acids of CETP. The Examiner's Answer ignores the claim language of the immediate predecessor application to the present application, which is now U.S. 6,555,113 (Tab C of the Brief). The claims of the '113 patent are directed to methods of using vaccine peptides defined in the same manner as the appealed claims, i.e., in its broadest aspects the claims are directed to peptides comprising "a helper T cell epitope portion linked to a B cell epitope portion, wherein said B cell epitope portion comprises a B cell epitope of CETP" (see Claim 1 of the '113 patent). The '113 patent furthermore includes a Claim 8, directed to "[a] method for altering the catabolism of HDL-cholesterol **to decrease the development of atherosclerotic lesions** in a human or other animal..." Appellants submit that the allowability of this embodiment is relevant to the appealed methods of preventing atherosclerosis.

Appellants' point is that, considered together, the '022 and the '113 patents demonstrate that the definitions of the vaccine peptides included in the claims on appeal have already been deemed fully enabled and adequately described by the USPTO. Thus, the only new facet raised in the present case is whether prevention of atherosclerosis is inadequately enabled and described although treatment of atherosclerosis or decreasing development of atherosclerotic lesions are apparently conceded to be fully enabled and adequately described.

The Examiner also points out that in the obviousness rejections there is an additional reference cited that was not cited in Appellants' earlier cases, namely U.S. 6,143,305 ("Stevens"). However, Appellants do not see how Stevens is not merely additive to the similar teachings of, e.g., Talwar, which also relates to attempting to actively immunize a subject against a self hormone, and which was of record during the prosecution of Appellants' predecessor applications.

The Stevens patent is asserted to teach "the advantage of active immunization over passive" as well as teaching that "to actively immunize a mammal against its own, 'self-antigen' was well known in the art and successfully applied for various classes of endogenous proteins." (Examiner's Answer at page 15.)

The Stevens patent is hardly the universal teaching of knowledge in the art concerning active immunization to overcome tolerance to self the Examiner asserts. Although modification of non-hormone proteins is mentioned as a possibility, the patent gives no description of a construct or an example of a construct except for modified reproductive hormones: human and baboon leuteinizing hormone, human and baboon chorionic gonadotropin, follicle stimulating hormone, and baboon placental lactogen. The point is that whereas "non-hormone protein" is mentioned in Stevens, there is no specific mention of CETP as a modulation target, so the Stevens reference is not seen to be a linking reference between the active immunization references that are unrelated to CETP or atherosclerosis and the CETP references which make no mention of active anti-self CETP as a concept for controlling endogenous CETP activity. Nor does Stevens show successful application of his modification techniques to any protein other than the hormones listed above. The addition of Stevens still leaves the person of ordinary skill in the art at the time of Appellants' invention without a suggestion in the art that native, endogenous CETP activity could be successfully addressed via active immunization using a hybrid vaccine peptide.

Accordingly, inclusion of the Stevens reference in the mosaic-like reference combinations of the final Office Action does not provide combined teachings significantly different from those already considered by this Board in reversing obviousness rejections in Appellants' grandparent application (Tab B of the Brief).

II. Enablement of Methods for Prevention of Atherosclerosis

With regard to enablement of prevention, the Examiner refers to the comparative data from Appellants' examples and then concludes:

> "One of skill in the art at the time the invention was made would clearly have interpreted these data as *reduction, not completely prevention* of atherosclerotic lesions in animals." (Examiner's Answer at page 16, emphasis in original.)

Appellants now understand that the Examiner is defining "prevention" of atherosclerosis as complete prevention of atherosclerotic lesions. Thus, the Examiner is arguing that his definition of a method of prevention is not enabled, rather than that the methods themselves are not enabled.

As Appellants have pointed out in their main Brief, atherosclerosis is a disease where treatment and prevention are intertwined. This is because atherosclerosis is a cumulative disorder, involving gradual build-up of plaque in the arteries. This plaque build-up, or development of atherosclerotic lesions, is a natural phenomenon that occurs in humans and other animals, but this development only reaches the pathological status of a disease when plaque accumulation threatens occlusion of an artery, with the attendant ischemia and thrombus formation that might be lethal. *See*, definition of atherosclerosis at Tab D of Appellant's Brief. Thus, "prevention of atherosclerosis" as it is understood in this art is prevention of the pathology of atherosclerotic plaque deposit, and with this understanding, a *reduction* in plaque formation or *retarding* the development of atherosclerotic lesions would be taken by those skilled in the art as prevention of atherosclerosis. Since the Examiner appears to acknowledge that reduction of atherosclerotic lesions is enabled by the specification, Appellants submit that the specification is enabling for methods of treating and preventing atherosclerosis.

The Examiner has introduced the Maillard reference as authority for his argument that methods of prevention are not enabled by Appellants' specification, stating:

> "Moreover, the current state of the art is that there is a lack in effective methods capable of preventing atherosclerosis-

> related conditions, as taught by Maillard et al." (Examiner's Answer at page 16.)

As alluded to by the Examiner at page 5 of the Answer, this statement is derived from the abstract of the Maillard reference, the first paragraph of which is reproduced below:

> "New therapeutic option: Atherosclerosis-related conditions are the primary cause of mortality in western countries. the incidence of severe limb-threatening ischemia of the lower limbs reaches 500 to 1000 per million inhabitants. The lack of effective treatment capable of preventing amputation in the most severe cases has led to research into the development of collateral circulation to replace the occluded arteries. Preclinical data has demonstrated that angiogenic factors can stimulate collateral circulation. This new therapeutic approach is called "angiogenesis therapy."

The remainder of the Maillard article relates to the role of VEGF in neovascularization and angiogenesis, and proposes the use of VEGF for angiogenesis therapy.

Appellants respectfully submit that the Maillard article is not authority for the principle put forth by the Examiner, i.e., that there is a lack of effective methods for preventing atherosclerosis *ergo* Appellants' claims to methods of prevention must not be enabled.

First, consideration of the entire first paragraph quoted above reveals that the Examiner has inaccurately paraphrased the abstract: The statement relating to a "lack in effective methods" by Maillard et al. does not apply generally to atherosclerosis-related conditions, rather the lack in effective methods relates to "treatment capable of preventing amputation in the most severe cases" of "severe limb-threatening ischemia". Thus, the Maillard reference does not contain the "teaching" that the Examiner asserts it does.

Second, Appellants challenge the assertion of the Examiner that such a sentence, even if it existed in Maillard, would be taken by those skilled in the art as evidence that would cause them to disbelieve the teachings of Appellants' disclosure. Such a broad statement, used to introduce an article having nothing to do with the subject of the present

invention, having nothing to do with cholesterol metabolism or regulating CETP activity, cannot be taken out of context and proposed as an illustration of the perception of the hypothetical person skilled in the art who intends to practice Appellants' invention. The person skilled in the art of Appellants' invention, after reading the entire specification of Appellants' application, would be enabled to practice all of the methods encompassed by the appealed claims, and would take Appellants' teachings as providing a reasonable basis for expecting that the prevention of atherosclerosis could be achieved applying the claimed methods. Moreover, this would still be the case if the same person skilled in the art was apprised of the first paragraph of the Maillard article, the entire Maillard article, or the interpretation of the Maillard article given by the Examiner.

III. Appellants' Full Possession of the Invention at the Time of Filing

In the Examiner's Answer, the Examiner has argued that one of skill in the art "would not envisage, based on the instant disclosure, the claimed method of treating or preventing atherosclerosis comprising [administering] vaccine peptide, wherein [the] vaccine peptide [comprises] a universal helper T cell epitope portion linked to any B cell epitope of CETP." (Examiner's Answer at page 18.) However, Appellants assert that that is PRECISELY what a person skilled in this art would envision on the basis of the present specification.

Appellants, after all, have set forth a conception of a hybrid antigenic peptide having two components: a universal helper T cell epitope portion and a CETP B cell epitope portion. For each component, several concrete examples are described and listed: for the helper T cell epitope, for example, a Markush group listing tetanus toxoid, diphtheria toxoid, pertussis vaccine, Bacile Calmette-Guerin (BCG), polio vaccine, measles vaccine, mumps vaccine, rubella vaccine, purified protein derivative of tuberculin, keyhole limpet hemocyanin, hsp70, and combinations thereof is given; and for the CETP B cell epitope portion, several particular examples are given including the peptide of amino acids 16-31 of SEQ ID NO:2, the peptide of amino acids 16-34 of SEQ ID NO:8, any six consecutive amino acids of the C-terminal 26 amino acids of human CETP (SEQ ID NO:1), and an antigenic index of the entire length of human CETP (Fig.

8A). And furthermore, Appellants have supplied a series of working examples demonstrating the synthesis of the vaccine peptide of SEQ ID NO:2 and its use according to the appealed claims to show treatment and prevention of atherosclerosis in test animals. With this wealth of teaching, it is indeed the fact that a person skilled in the art would accurately envisage, based on the instant disclosure, how to make and use the full range of described vaccine peptides comprising the required two components, and that Appellants were in full possession of their inventive concept at the time they filed their application.

The Examiner argues that "the patent [application] merely describes the desired function of the compound called for but contains no information by which a person [skilled] in the art would understand that the inventors possessed the claimed invention." (Examiner's Answer at page 18.)

It is incorrect to say that the vaccine peptides are described only in terms of a desired function or that the application contains "no information" by which a person skilled in the art would understand possession of the invention by Appellants. Reference is made to the structural information cited above for both required components of the vaccine peptides. This is not merely functional and is not correctly characterized as "no information".

It is a fact that there are functional concepts recited in the claims, i.e., "antigenic" and "B cell epitope", however these terms are expressly defined in the specification or are well known terms of art in the field to which this invention pertains, and thus a person skilled in this art understands the metes and bounds of what is being claimed. Moreover, the inclusion of functional terms in the claims does not prevent understanding of the invention: The person skilled in the art is not required to practice the invention by referring only to the claims; rather, the entire specification and all its examples are available to aid in understanding what is claimed and what the inventor possessed at the time of filing.

The Examiner makes several references to *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993) to support the contention that Appellants' written description is inadequate to show possession of the methods of the appealed claims. However, that case related to

whether an applicant could claim DNA specifically encoding beta interferon without first sequencing the DNA to determine that the correct DNA had actually been isolated. The CAFC held that for claiming DNA specifically encoding a protein, the conception of the invention and the reduction to practice by sequencing the DNA occurred at the same moment. That is not the case here: Appellants' disclosure describes the concept of the invention and provides a reduction to practice using a peptide defined by amino acid sequence. Then multiple concrete alternative examples are described with reference to known structures and known immunological properties. From this, a person skilled in the art is provided with a full and detailed vision of what Appellants' invention is and is fully apprised that such invention was in Appellants' possession at the time the present application was filed.

IV. A. The References Relied on by the Examiner are Improperly Combined

In response to Appellants' points distinguishing the primary and secondary references, the Examiner points out that non-obviousness cannot be shown by attacking references individually where the rejections are based on a combination, citing *In re Young*, 403 F.2d 759, 150 USPQ 725 (CCPA 1968). Appellants are aware that the reference combination must be addressed, but they point out that it is not possible to discuss the sum of a reference combination without discussing the contents of each reference. Following the an analysis of the individual primary and secondary references, Appellants do make the following point in their Brief:

> "From no combination of these references is the desirability of CETP as an autoimmune target suggested, and even the presence of a reference (Stevens) that involves attempts to raise an antigen response to a self antigen does not contain anything to encourage the person of ordinary skill in the art to apply the Stevens disclosure respecting hormones to a completely different class of protein, i.e., a large, constitutively produced, circulating serum protein that plays a role in a complex metabolic cascade, that is, CETP." (Brief at 31.)

Appellants' point is that the combination of references taken together fails to identify CETP as a potential autoimmune target, leaving aside the failure of any

combination to propose an antigenic vaccine peptide that could accomplish autoimmune control of CETP activity or to suggest an autoimmune response of sufficient magnitude and duration to prevent development of atherosclerosis.

Appellants emphasize that the very idea of devising an immunogen to cause the endogenous CETP of a subject to be recognized by its own antibodies, where it previously was not, is an idea that is utterly absent from the citations of record. The Examiner places great emphasis on the mention of Stevens of non-hormone proteins, but the term "non-hormone protein" does not directly conjure up CETP, and no more relevant discussion relating or leading to CETP or atherosclerosis is contained in Stevens.

Moreover, Stevens himself recognizes the unpredictability inherent in breaking tolerance to self proteins, and expresses several warnings:

> "Such immunization represents an effective fertility control technique, *provided no physiological consequences are encountered which may be found to react adversely to the performance of other body constituents.*" (Stevens reference at col. 11, lines 26 et seq., emphasis added.)

> "One important consideration which should always be borne in mind in choosing a polypeptide for modification by the instant invention is the problem of cross-reactivity. As well known to those skilled in the field of immunology, it is not uncommon to find that antibodies intended to react with one protein (the 'target' protein) also react to a significant extent with other, non-target proteins. *This is a serious problem, since it may cause the administration of a modified polypeptide intended to provoke the formation of antibodies to one specific natural hormone to cause the generation of antibodies to one or more other hormones, which it is not desired to effect. In some cases, the reactions with the non-target proteins may cause damage to essential body functions.*" (Stevens reference at col. 12, lines 54 et seq., emphasis added.)

Thus, the message of Stevens is that when considering another endogenous target, unforeseen problems such as cross-reactivity with unintended endogenous targets or impairment of the performance of other body constituents may result. In view of this

Stevens teaching, the mention of non-hormone proteins as potential targets cannot be interpreted as a suggestion that the Stevens teaching can be successfully applied to all other proteins: Stevens himself states that this is not so. Moreover, Stevens' teachings quoted above underscore Appellants' point that the art of immunology is not so predictable that the success of every selected non-hormone target will be similar to the results demonstrated with reproductive hormone targets. In fact, Appellants' Brief contains scientific reasons why teachings relating to one immunological target would not be extrapolated to another target by a person of ordinary skill in the art. *See*, e.g., Brief at page 31 and Michel et al. reference of record, discussed at pages 37-40.

IV. B. No Combination of Any of the Examiner's Citations Shows or Suggests Successful Treatment or Prevention of Atherosclerosis

In the Examiner's Answer at page 23, the Examiner disagrees with Appellants' interpretation of Swenson, stating that Swenson explicitly teaches that the activity of CETP could have an important influence on atherosclerosis. This is indeed a statement in the introductory paragraph to the Swenson reference, and there is no dispute that the function of CETP in HDL-cholesterol metabolism was known at the time of Appellants' invention. However, Appellants' points with respect to Swenson were (a) that whereas Swenson speculates that the activity of CETP "could" have an effect on atherosclerosis, it was Appellants who actually proved that control of CETP activity has a direct effect on atherosclerotic plaque deposit, (b) that although Swenson discussed the neutralization of CETP activity *in vitro*, there is no proposal in Swenson to regulate CETP activity *in vivo* via autoimmunization, and (c) none of the neutralization of activity data of Swenson (or any other reference of record) shows actual prevention of atherosclerosis -- meaning that the most that can be suggested from any combination of the references is that attempts to control CETP activity *in vivo* by autoimmunization would be obvious to try, not obvious. It is axiomatic that obvious-to-try is not sufficient to find obviousness under 35 U.S.C. §103. *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987); *Ex parte Olde*, 229 USPQ 196 (BPAI 1985).

In the Examiner's Answer, page 24, it is argued that the short duration of the effects of passive immunization shown in Whitlock would have been expected by a

person of ordinary skill in the art, and that this would be automatically compensated for by switching to active immunization against a self protein in the manner of Stevens. The Examiner concludes that "the increase in duration of modulation of CETP activity using active immunization with antigenic peptide would have been an obvious variation of Whitlock et al., because both passive immunization as taught by Whitlock et al., and active immunization taught [by the] current application, the motivation was the same -- to target the endogenous CETP that would be beneficial in treating atherosclerosis."

Appellants referred to the short duration of passive immunity in Whitlock to underscore the lack of suggestion available to the person of ordinary skill in the art without the benefit of Appellants' data. The Examiner is arguing that the duration of immunity achieved by Appellants would be the natural result of active immunization, but that conclusion is not based on any fact in the prior art. Rather, there is no data in the prior art to speculate on whether active immunization against CETP would result in an antibody response at all, whether it would result in harmful cross-reactivity (as cautioned by Stevens), or whether actively induced autoimmunity would be of sufficient duration to have an effect on atherosclerosis. Although Appellants demonstrated that active immunization against self CETP was feasible and that it endured long enough to affect atherosclerosis, those facts were not known to a person of ordinary skill in the art at the time of Appellants' invention, and they cannot be predicted from the data vacuum of the references of record.

IV. C. The Evidence of Record Shows the Lack of a Reasonable Expectation of Success in Active Immunization Against Self Proteins

In Section IV.C. of the Brief, Appellants argue that even if the teachings of the references cited by the Examiner are combined, the combinations still fail to establish obviousness of Appellants' invention, because the combinations fail to provide a person of ordinary skill in the art with a reasonable likelihood of success for treating or preventing atherosclerosis. Appellants point out that the prior art must not only suggest that the claimed methods should be performed but must also suggest that in so performing the methods there is a reasonable expectation of success, relying on *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir.1988) and *In re Vaeck*, 947

F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). The Examiner counters by emphasizing that the Stevens reference establishes that it well known how to actively immunize against a self-antigen and that the Stevens teaching applies to "various classes of endogenous proteins". (Examiner's Answer at page 25.)

Appellants have shown elsewhere in this Reply Brief that Stevens is not a universal predictor of success in active immunization against self. Moreover, the mention of non-hormone proteins capable of modification according to Stevens does not include mention of CETP, and the mention of conditions other than regulation of pregnancy in Stevens does not include mention of treating atherosclerosis or inhibiting CETP activity. Moreover, the Stevens patent contains direct teachings that success in selecting alternative autoimmune targets is unpredictable and cautions against possible harmful effects. Accordingly, the Examiner's reliance on Stevens is not persuasive that the success obtained by Appellants would have been obvious to a person of ordinary skill in this art prior to Appellants' disclosure.

Appellants rely on Michel et al. (of record) as a demonstration that successful use of passive immunization is not predictive of success of active immunization. Passive immunization involves administration of non-endogenous antibodies raised *ex vivo* against a particular target; active immunization involves induction of an endogenous immune response wherein endogenous antibodies are produced that recognize a particular target. Where active immunization is directed against an endogenous target, normal immune tolerance of the endogenous target must be circumvented. Michel et al. reviews several examples demonstrating how the results of studies using passive immunity against a protein are not capable of providing the person of ordinary skill in the art with any reasonable basis for predicting the outcome of an attempt to actively immunize an individual against the same protein.

The Examiner counters that such unpredictability is obviated by Swenson, which shows that CETP and CETP fragments are immunogenic. However, as pointed out in the Brief, Swenson immunizes mice with human CETP and fragments of human CETP. The antibody response is not against endogenous murine CETP but against foreign, human

CETP. An active immunization that elicits murine antibodies capable of recognizing murine CETP *is not shown.*

The Examiner also argues that "Swenson teaches a[n] immunogenic peptide that is the exact the same length and composition as amino acid sequence of SEQ ID NO:1..." (Examiner's Answer at page 26.) Appellants point out that SEQ ID NO:1 is not an immunogenic peptide, and it is not an antigenic peptide according to Appellants' invention; it is merely the C-terminal 26 amino acids of human CETP.

The Examiner goes on to argue that Swenson reveals a peptide that has "the same amino acid sequence as amino acid numbers 16-31 of SEQ ID NO:2 that was successfully used to generate production of antibody to recognize endogenous CETP." Appellants point out that while Swenson discusses the C-terminal 26 amino acids of CETP, the specific CETP 16-mer found in SEQ ID NO:2 is not described, nor is the 31-mer hybrid sequence of SEQ ID NO:2 which is an embodiment of Appellants' invention. Moreover, the fact that SEQ ID NO:2 was successfully used to generate antibodies recognizing endogenous CETP is not a fact in the prior art but a fact only in Appellants' disclosure, and thus the Examiner cannot bootstrap the disclosures of the references using it.

IV. D. With Respect to Treatment and Prevention of Atherosclerosis by Active Immunization, Appellants' Results Are Unexpected and Therefore Indicative of Non-Obviousness

In Section IV.D. of their Brief, Appellants argue that even if the references of record are combined as proposed by the Examiner, the person of ordinary skill in this art could not have expected the results as demonstrated by the various examples in the specification. Without the benefit of Appellants' disclosure, a person of ordinary skill in this art could never predict that a sustained autoantibody response against endogenous CETP could be induced or predict that the sustained response would last long enough to alter lipoprotein levels and prevent development of atherosclerotic lesions in the vaccinated individual. Considering the short-lived passive immunity of Whitlock, the long-term results demonstrated by Appellants, and their effect on atherosclerosis, would

have been unexpected results to a person of ordinary skill in the art, indicating non-obviousness of Appellants' methods.

The Examiner counters, as before, that the short-lived effect of Whitlock would have been expected by the person of ordinary skill and would have been cured by following the teaching of Stevens to use active immunization:

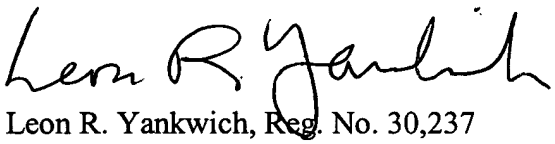
> "Clearly the teaching of [Stevens] would be the 'spark of motivation' to one [of ordinary skill] in the art to consider endogenous CETP as a target for endogenous immune regulation." (Examiner's Answer at pages 27-28.)

Appellants submit that the Examiner is answering the demonstration of unexpected results by arguing that it would have been obvious to try CETP as an active immunization target to overcome the deficiency of passive immunization shown by Whitlock. Even if it is accepted that a person of ordinary skill in the art would have been led by the combined references to design an antigenic vaccine peptide as described by Appellants and use it to actively immunize a subject with the aim of controlling native CETP activity, there is simply no basis for predicting the results achieved by Appellants at the time of Appellants' invention and without knowledge of Appellants' success. Thus, the results achieved by Appellants are unpredictable and unexpected, and the methods claimed must be considered non-obvious over the prior art.

CONCLUSION

For reasons set forth above and in Appellants Brief on Appeal, the final rejections applied against appealed Claims 28, 29, and 37-39 under 35 U.S.C. §112, first paragraph, and under 35 U.S.C. §103(a) as set forth in the final Office Action of April 22, 2003 are in error and should be reversed by this Board.

Respectfully submitted,



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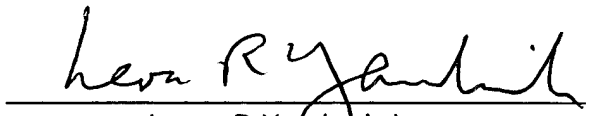

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